Journal of Neuroscience Methods 376 (2022) 109611

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Nonhuman primate models of ischemic stroke and neurological evaluation after stroke

Xiao Lin [a,b], Hua Wang [a,b], Jiayu Chen [a,b], Peiqi Zhao [a,b], Min Wen [c], Lebohang Anesu Bingwa [a,b], Kunlin Jin [d], Qichuan Zhuge [a,b,*], Su Yang [a,b,*]

[a] Department of Neurosurgery, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, PR China
[b] Zhejiang Provincial Key Laboratory of Aging and Neurological Disorder Research, Wenzhou Medical University, Wenzhou, Zhejiang 325000, P.R. China
[c] Department of Neurology, Guangzhou First People's Hospital, Guangzhou 510000, China
[d] University of North Texas Health Science Center, Fort Worth, TX 76107, United States

ARTICLE INFO

Keywords:
Nonhuman primates
Ischemia stroke
MCAO
Neurological evaluation

ABSTRACT

Nonhuman primates are closer to human beings than rodents in genetics, neuroanatomy, physiology and immunology. Nonhuman primates are therefore considered an ideal preclinical model to replicate various aspects of human stroke. Ischemia stroke models in nonhuman primates can better fit the physiological symptoms and changes in humans after cerebral ischemia. Currently, various construction methods and neurological evaluation methods have been developed and applied to stroke models of nonhuman primates, including craniectomy models, endovascular stroke models, autologous thrombus models and intraluminal filament models. Meanwhile, new innovative methods have emerged, such as the endothelin-1 model and photothrombosis model. In the past thirty years, these model studies have explored various mechanisms that are initiated in the first minutes, hours, and days after a stroke. Permanent and temporary middle cerebral artery occlusion models have been trying to simulate the complex situation of human stroke. However, a comprehensive comparison of the above methods, including their advantages and disadvantages, difficulty and application fields, is limited. Here, we introduce various modeling methods that are currently available for nonhuman primate stroke models, compare the differences between these different preparation methods, and analyze the advantages and disadvantages of the various methods and the fields of application. The imaging detection methods of nonhuman primates after cerebral ischemia and the neurological evaluation methods after stroke are also discussed briefly. Methods are sorted and compared so that scholars can choose appropriate modeling methods and evaluation methods to establish nonhuman primate stroke models.

1. Introduction

Every year worldwide, 15 million people suffer from stroke, resulting in 5 million deaths, and another 5 million people are permanently disabled. Stroke is the main cause of long-term disability in the United States, and more than half of stroke survivors over 65 years old have limited mobility (Nikolas and Toman, 2019). Ischemic stroke accounts for more than half of the current stroke cases and has become the main cause of death and disability in patients without effective treatment (Valery and Feigin, 2015). Stroke is caused by thromboembolic occlusion of the cerebral aorta or its branches. Vascular occlusion leads to hypoxia and loss of energy, followed by the formation of reactive oxygen species, the release of glutamate, the accumulation of intracellular calcium, and the induction of inflammatory processes (Christopher et al., 2012). Eventually, irreversible damage to the brain tissue occurs in this area. The main treatment method is the use of neuroprotective drugs and thrombolysis drugs. However, currently approved thrombolysis drugs that can be used for acute ischemic stroke are very limited. The only one permitted by the Food and Drug Administration (FDA) and used in stroke is recombinant tissue plasminogen activator (rt-PA). If the application time exceeds 4.5 h, it is basically invalid and will increase the risk of hemorrhage (Maarten and Lansberg, 2009). This has resulted in 90% of patients being unable to be treated with thrombolytic drugs in time (Gregg et al., 2011). Therefore, there is an urgent need to develop new thrombolytic drugs or extend the effective time of existing drugs.

Developing new thrombolytic drugs requires the use of appropriate

* Corresponding authors at: Department of Neurosurgery, First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325000, PR China
E-mail addresses: qc.zhuge@wmu.edu.cn (Q. Zhuge), yangsu@wmu.edu.cn (S. Yang).

https://doi.org/10.1016/j.jneumeth.2022.109611
Received 11 January 2022; Received in revised form 20 April 2022; Accepted 22 April 2022
Available online 26 April 2022

animal thrombosis models. Rodents (rats, mice) are widely used in medical research for studying cerebral ischemia, by the beneficial of its low cost, abundant sources, and simplicity of operation (Jiangnan et al., 2018; Li Cai et al., 2020). Many treatment strategies have been proved working after stroke in rodents, but have not been successful in clinical translation. The main reason for the failure is large differences between the brains of rodents and humans, causing rodents to respond differently to the same ischemic damage. Large animals (such as pigs, canines, nonhuman primates) are similar to humans in genetic background, behavioral characteristics, risk factors for cerebrovascular disease, anatomy of brain tissue and blood vessels (Bin Cai, 2016). Therefore, large animals more closely resemble the pathophysiology and clinical manifestations of stroke in humans. Generally, different volume of white matter and gray matter triggers different sensitivities to cerebral ischemia, and larger brain tissue is suitable for complex surgical operations and facilitates postoperative imaging evaluation. At the same time, large animals, especially nonhuman primates (NHPs), have corresponding neurological dysfunction after stroke, which is very suitable for the observation of stroke treatment and rehabilitation process. However, the research of large animals also has certain limitations, such as high cost and certain ethical issues, and requires relatively sophisticated testing equipment. Therefore, it is very difficult to select the most suitable animal to study stroke among many experimental animals. Nonhuman primates (macaque, baboons, etc.) are closer to humans than rodents in physiological structure and blood vessel supply of the brain. At present, due to the limits of economic and ethical factors, the main application areas of nonhuman primate models are limited. However, researchers using NHP models have got the important achievements of the pathogenesis and the recovery of the treatment, especially about major diseases that currently affect human health, such as human viral infections, respiratory disease, diabetes, stroke and neuroprotection, etc (Brenchley, 2018; Lisa et al., 2017; Douglas and Cook, 2012; Haitao Zhu et al., 2014). Cerebral ischemia stroke models in NHPs can better fit the physiological symptoms and changes in humans after cerebral ischemia, meaning this option has become the best choice for studying human stroke disease. The distribution area of the middle cerebral artery (MCA) is also similar to that of humans, and the size of the brain is quite suitable for magnetic resonance imaging (MRI) research (Maxime Gauberti et al., 2012); therefore, numerous scientists have used nonhuman primates to simulate human brain disease (Gregory et al., 1985; Go Kito et al., 2001).

In neuroscience, NHPs are often used to prepare ischemic stroke models (mostly the macaque and baboon) because they have an intelligence quotient. NHPs can use their arms to handle various tools to complete motor tasks. Because of their degree of compliance and irritability after training, the evaluation of neurological function in an ischemic stroke model can be closer to that in real clinical patients (Jonathan et al., 2001). Therefore, more NHPs are being used to study various poststroke treatment methods, such as acute and chronic drug treatments and stem cell treatments after cerebral ischemia (Atsuhiro Sugidachi et al., 2016; Jiamei Lia et al., 2010). After establishing the model, researchers then use neurological behavioral tests and imaging tests to evaluate the treatment effects (Justine Debatisse et al., 2020). The middle cerebral artery is a frequent site of cerebral ischemia in humans, and many cerebral ischemia models have been developed for MCA. At present, the method of establishing NHP models of local cerebral ischemia can be subdivided into the transorbital approach method, transcranial approach method, balloon compression model, snare ligature model, etc. Although different methods can lead to stroke, the applicable research field is different.

This article briefly introduces the modeling methods of several NHP models of focal cerebral ischemia and briefly describes their advantages and disadvantages. Simultaneously, based on the model preparation results, this article sorted the evaluation method of imaging and neurological function in NHPs after cerebral ischemia.

2. Methods of nonhuman primate ischemia stroke models

2.1. Craniectomy model

2.1.1. Transorbital approach method (Clamp model)

The earliest established NHP stroke model was the operation through the orbital approach. In 1970, Hudgins first established this model in squirrel monkeys, which removed the eyeball, periorbital tissue, and optic nerve during the operation (WR and Garcia, 1970). After, the skull on the posterior orbital wall was removed to expose the anterior part of the circle of Wills, the squirrel monkey's middle cerebral artery was identified, and an arterial clip was used to block the proximal M1 segment of the MCA. Then, in 1975, Symon used the orbital approach method in baboon but blocked the proximal M1 and distal M1 of the MCA to compare the difference between these two segments (L S, 1975). To date, this method has been applied to large NHPs through the orbital approach. In 1992, Liu and Symon again used this method to block the bilateral A1 in baboon, which aimed to test the blood of the territory of the anterior cerebral artery (Liu et al., 1992). Before 1997, researchers only used a transorbital approach to permanently clamp the cerebral artery. Research on ischemia–reperfusion in the brains of NHPs is still lacking. Young anesthetized baboons were subjected to 6 h of either reversible or permanent middle cerebral artery occlusion. The results confirmed that early reestablishment of cerebral blood flow after focal ischemic insult is not detrimental but indeed is beneficial regarding the final infarct volume (Alan et al., 1997). Then, in 2008, Murphy chose to clamp the M1 segment of the MCA, and after 90 min, the methods were not changed, thereby forming an ischemia–reperfusion model in male and female rhesus macaques (Stephanie et al., 2008). Magnetic resonance angiography (MRA) technology was then used to identify cerebral infarction differences between sexes. At present, the transorbital approach method is used both to study permanent occlusion of blood flow and ischemia–reperfusion in the NHP brain. The ischemia time can be adjusted according to the needs of the research and remains a popular method of modeling a stroke in NHPs. The transorbital approach is better than other techniques requiring a craniotomy for exposure of the middle cerebral artery, which leaves a significant residual dural defect. The transorbital approach requires less operation time with decreased attendant morbidity and mortality. In addition, vascular structures are not disrupted by this method, in contrast to the other craniotomy approach (Shunichi Fukuda, 2003).

2.1.2. Transcranial approach method (electrocoagulation model)

This method emerged because the blood vessels in the deeper parts of the brain cannot be reached through the transorbital approach; for example, in the M2 segment of the middle cerebral artery and the transorbital approach, the available operation space is too small, it easily damages the surrounding tissue, and the failure rate is high. This method uses a lateral transcranial approach to open the skull and incise into the corresponding area of tissue to expose the artery and operate on it. After entry from the pterion (left side or right side), the subcutaneous tissue is cut, and the flap is turned to the sphenoid pterion. After cutting the meninges, the brain is gently retracted to expose the lateral fissure. After carefully dissecting the subarachnoid space and trabecula of the related brain cistern under an operating microscope, the target artery is gradually exposed without affecting the brain tissue. Then, operations such as electrocoagulation of the artery (clamp can also be used to block the artery so that ischemia–reperfusion can be performed). In 1996, Marshall first used electrocoagulation through the lateral transcranial approach to permanently occlude the M2 segment of the middle cerebral artery in marmosets (Ridley, 1996), which showed that all subjects showed unilateral dyskinesia of the contralateral forelimb and neglected contralateral tactile stimuli. Then, in 2003, Jonathan improved their original method by using a monkey stereotactic frame to fix the marmoset brain. The position of electrocoagulation is adjusted from the M2 segment to the M1 segment (Ridley, 2003). Because the occlusion is

located in front of the lenticular artery, it blocks blood flow to the entire MCA area, including the subcortical structure, caudate nucleus, and putamen. Subsequently, scholars used this method as the basis for their research, using electrocoagulation or clamp blockade of blood flow to establish vascular occlusion through a transcranial approach (Bruno et al., 2019; Henry et al., 2017; Douglas et al., 2012). In the same postoperative cynomolgus monkeys, a distal occlusion of the M1 branch of the middle cerebral artery occurred, and an infarction of the same size was observed, mainly involving the cerebral cortex and subcortical white matter distributed along the middle cerebral artery (Xinran Chena et al., 2015). Monkeys with partial middle cerebral artery occlusion and stable infarct areas have been observed mainly in the basal ganglia and subcortical areas. A transcranial approach to occlude the artery greatly broadens the operating range and enables the establishment of various ischemia models. This model is suitable for studying secondary damage in remote regions or drugs that have neuroprotective effects after stroke. However, the mechanism of blocking blood vessels by electrocoagulation or clamp is significantly different from the pathogenesis of human cerebrovascular embolism, and blocked blood vessels cannot be used for drug thrombolysis or mechanical recanalization experiments after vascular embolization. Additionally, this method is demanding and can easily result in bleeding or other injuries during the operation.

2.1.3. Balloon compression model of MCAO

The balloon compression model, as the name suggests, uses a special airbag to wrap the separated middle cerebral artery. After exposure of the targeted cerebral artery, the airbag is inflated to pressurize the blood vessel and physically and mechanically block blood flow. In 1980, Spetzler first used this method in a baboon; the middle cerebral artery was first separated by the transorbital approach, and an inflatable balloon around the middle cerebral artery was then wrapped (Spetzler et al., 1980). The inflated balloon causes vascular occlusion by mechanically compressing the blood vessel. After 1–30 min (different times according to the ischemia reperfusion requirement) of temporary occlusion, the balloon was removed for subsequent testing. The balloon blocking method depends solely on external physical and mechanical forces, which differ from middle cerebral artery occlusion (MCAO) in humans, and its physiological and pathological mechanisms are also inconsistent. Meanwhile, the airbag has a serious impact on the surrounding tissues and may cause mechanical damage to blood vessels. All of these disadvantages limit its use. Moreover, the effect of the balloon can be achieved using a micro arterial clip, so the method has gradually been replaced.

2.1.4. Snare ligature model of MCAO

In 1981, Crowell invented this method to temporarily block the middle cerebral artery in macaques using a specific snare ligature (Crowell et al., 1981). The method is operated at the base of the brain after the transorbital approach, requires separation of the middle cerebral artery, connecting a silk thread and corresponding catheter, and then exposing the silk to the wound and suturing the skin. The eyeball also needs to be removed. This model has several advantages. Most importantly, it avoids the huge trauma caused by transcranial approach craniotomy, minimized the trauma by using a special ligature implanted in the orbit. There is less damage than mechanical or balloon compression equipment. Another advantage is that it permits reperfusion in awake monkeys, which releases occlusion by refining the snare ligature design. However, the disadvantages are also obvious, as it is expensive and requires extremely high surgical operation skill. These shortcomings limit its application in NHP cerebral ischemia models.

2.2. Endovascular stroke model of MCAO

Endovascular stroke models usually use interventional methods, and various emboli are applied to induce cerebral artery embolism models, such as using coils or wires to block blood vessels or utilizing an inflating balloon to block blood vessels endogenously. In 1974, Molinari first used the endovascular stroke model in macaque mulatto, in which the embolus is not a coil or wire but a small amount of silicone rubber compound and the size was fixed (1.6 mm) (By et al., 1974). However, in that era, digital subtraction angiography (DSA) was developed slowly, and DSA was not used to confirm the location of the embolus, but a palpable pressure drops signaled clearance of the embolus from the cannula into the internal carotid artery. Finally, a monkey stroke model was successfully formed but where the embolus entered could not be accurately determined, and there may be a risk of blood vessel rupture caused by over injection of the embolus. Subsequently, the embolus was gradually replaced with a detachable coil and a retractable airbag. Subsequent development of DSA helped determine the exact location of the embolism in this intervention.

At present, the most classical and interventional method is to insert a catheter percutaneously through the femoral artery under angiography or enter the internal carotid artery. After reaching the internal carotid artery, the guidewire in the catheter is withdrawn. The micro guidewire is used to introduce the tip of the catheter into the M1 segment of the middle cerebral artery, and a contrast agent is used to confirm the distance of the catheter tip to the MCA. A detachable coil is inserted for temporary occlusion. After occlusion of the MCA with imaging methods, the embolus is then removed or stays in the blood vessels permanently according to the closure time required by the surgeon. DSA is employed to confirm the recanalization of the blood vessel (Makoto Sasaki et al., 2010). Another embolus is an endogenous balloon, which utilizes a special airbag after entering the intracranial artery of the macaque through the catheter that can temporarily inflate to block the blood vessel in the artery. Then, the airbag is deflated and removed when the ischemic time is sufficient (it differs from balloon wrapping the artery; this method, the airbag is located in the artery) (Di Wu et al., 2016). Similarly, some researchers separate the internal carotid artery and enter the MCA through a catheter directly (Huanmin Gao et al., 2006). It is worth mentioned that Tong using the trapping technique to deliver the 4–0 silk suture instead the coils to occlusion the MCA-M3 and MCA-M1 segments of rhesus monkeys, which effectively eliminates retrograde collateral flow in the MCA branch and produced consistent infarct results (Tong et al., 2015).

In brief, the most common embolus to induce an MCAO model in NHPs with the use of balloons, guidewires, coils and silk to block the MCA has advantages and disadvantages. The balloon is easy to control and completely blocks the lumen of the blood vessel but is difficult to manipulate and is not suitable for bending in the cerebrovascular system, making it difficult to reach blood vessels with a smaller diameter, and it is not suitable for the study of hypothermic treatment after ischemia–reperfusion (the balloon is blind and cannot be filled with refrigerant). There is a risk of rupture of blood vessels. The wire has a constant diameter, making it difficult to fit various vessel diameters; therefore, the same position of the guidewire may lead to different embolization locations in blood vessels. The coil is relatively soft, easy to operate, and can be accurately positioned. Apart from the cost factor, the wire has certain advantages compared to other occlusion methods. Silk is easy to obtain and costs less than coils. Because of its smaller diameter, it allows to accessed to finer sections of the middle cerebral artery, such as the M2 and M3 sections. Of course, because it is too soft, it needs more research to confirm whether occlusion is stable if only to use silk occludes the initial segment (M1) of middle cerebral artery. Although the endovascular stroke model of MCAO has certain shortcomings, compared with the orbital approach and craniotomy, this method does not require craniotomy and can be operated on by nonsurgical personnel, so it has been widely used. Justine used coil on cynomolgus macaques to simulate ischemia-reperfusion injury in the middle cerebral artery and developed the nonhuman primates neurological scale: (NHPNS) for evaluating monkeys after stroke. He evaluated the macaque's stroke per-occlusion and post-recanalization impairment on PET-MRI, in addition to acute and chronic neuro-functional assessment

(Justine Debatisse et al., 2020). Kyung used the endovascular stroke model to demonstrate that ischemic brain tissue could be salvaged after recanalization of the occluded artery (within 3 h), which with diffusion–perfusion matching (Kyung Sik Yi et al., 2017). Zhang used silk to occlude rhesus monkeys MCA-M2 and examined diffusion weighted imaging (DWI) and T2-MRI at 1–6 h and 48 and 96 h after post-occlusion, confirming that the diffusion-perfusion mismatch was visible generally at 6 h but nearly diminished at 48 h post occlusion (Xiaodong Zhang et al., 2015). In short, endovascular stroke model as a widely used method is suitable for research ischemia-reperfusion after stroke.

2.3. Intraluminal filament model of MCAO

This method was originally only used in rat MCAO models. In 1989, Enrique established this method in the rat middle cerebral artery (Longa et al., 1989). The most important procedure is introducing a 4–0 nylon intraluminal suture into the internal carotid artery (ICA) and advancing it to the MCA to block blood flow. Now, scholars apply this method to monkeys and imitate the same steps. In 2008, Thomas first used an intraluminal filament model in marmosets, and the common carotid artery of monkeys was separated through a median neck incision (Thomas Freret et al., 2007). After blocking the blood flow by ligating the distal end of the external carotid artery, the special nylon embolus was slowly inserted into the blood vessel from the proximal end of the external carotid artery. The blocking site in the middle cerebral artery was confirmed using a doppler blood flow instrument. After blockage with a specific embolization time, the nylon embolus is then withdrawn. Ebeline compared the difference between permanent and transient chronic ischemic stroke in marmosets based on this method (Bihel Ebeline et al., 2009). The results showed that neurogenesis was increased in both permanent and transient animals. After a marmoset stroke, permanent MCAO causes more severe sensorimotor impairment than temporary MCAO in the long-term. The advantage of the intraluminal filament model of MCAO is that it can strictly control ischemic time, and the embolus can be easily removed to obtain reperfusion with no transcranial operation. This method has lower requirements for operators and is easy to learn. By adopting this method, the animals have less traumatic injury and no obvious adverse reactions. The surgical procedure was achieved directly without postoperative mortality or cerebral hemorrhage. This method can ideally simulate various physiological reactions in cerebral ischemia patients after embolization and thrombolysis and has been widely used in stroke research on NHPs. The only disadvantage is that it damages the external carotid artery and affects the blood supply parts of the external carotid artery, such as the face, which may cause facial muscle paralysis after surgery.

2.4. Autologous thrombus model of MCAO

The autologous thrombus method requires a certain catheter for delivery. Venous blood from the animal must be collected before the operation and prepared in vitro into white thrombi of the required length using thrombin. In 2001, Kito first used autologous thrombus to model a cynomolgus monkey stroke (Go Kito et al., 2001). Thrombus occurs through the internal carotid artery injected into a specific location using a catheter and saline, leading to the thromboembolism model. Notably, autologous thrombi can be injected into the brain via the femoral vein catheter or directly through the internal carotid artery to localize to the MCA in rhesus monkeys and cynomolgus monkeys (Di Wu et al., 2016; Tetsuya Yoshikawa et al., 2008). The difference between these two approaches is that the former must be navigated by DSA; because the arteries that pass from the femoral artery to the internal carotid artery have a complicated shape, it would be impossible to reach without DSA. The thrombus is delivered after guiding the catheter to the aim artery. The latter does not require the help of DSA and only needs to enter a fixed length to reach the middle cerebral artery. In 2006, Kito used this autologous thrombus model of MCAO cynomolgus monkeys again to test whether urokinase dissolves blood clots in stroke and improves neurological function after stroke (Teruo Susumu et al., 2006). There are numerous and meaningful studies using this method. Wu used autologous thrombus to establish a rhesus monkey stroke model, and compared the differences between the stroke models established by the endovascular stroke model (balloon method) and autologous thrombus model (Longfei Wu et al., 2020). It confirms the advantages of the thrombus model include clinically translatable pathogenesis, relatively small infarct size, better survival and the possibility of thrombolytic therapy. The disadvantage of thrombus injection method is technical complexity and poor control over the exact location of occlusion. Based on autologous thrombus model, Song found that remote ischemic conditioning results in significant modulations of the plasma proteome in rhesus monkeys (Siying Song et al., 2021). Infarct formation with autologous thrombus model is the closest to clinical cases. Therefore, it has practical value in preclinical applications for the research, diagnosis, and treatment of the occurrence and development mechanism of stroke, especially thrombolytic therapy. In addition, the autologous thrombus model can be used in ischemia–reperfusion(I/R) studies, and the clots can also be indwelled to form a permanent vascular occlusion model if the blood clot ends up in the blood vessel without thrombolysis or withdraw it.

2.5. New thrombus induction method and prospects

2.5.1. Photothrombosis model of MCAO

At present, in addition to conventional physical methods to induce the middle cerebral artery, there are also methods utilizing a photothrombosis model of MCAO in NHPs. Photothrombosis is a newly discovered method in the last twenty years that can use a specific light source to illuminate the dye to form a local thrombus. Rose bengal, a photosensitive dye, was infused intravenously via the femoral vein and then circulated throughout the body. When irradiated by a cold light source, the dye is activated and causes endothelial damage, platelet activation and thrombosis, leading to local blood flow interruption. A photothrombosis model was first used to establish stroke models in rats because the method is simple and does not require complicated operations such as embolization or clipping. In 2005, Masashi first used this method in cynomolgus monkeys (Masashi Maeda et al., 2005). The photo illuminate dye on the surface of the middle cerebral artery for 20 min resulted in cyclical flow reduction (CFR), which produced a significantly larger infarction and more severe neurological deficits compared with clamp model, even though the decline in blood flow was smaller. Later, Tomizawa confirmed that the thrombus formed by a photothrombosis model of MCAO can be dissolved by drugs and improved thrombus formation and hemodynamic changes (Atsuyuki Tomizawa et al., 2015). These applications showed that the focal cerebral ischemia model made by rose-bengal dye irradiated with cold light produced changes in nerve function, such as consciousness disorder and limb movement disorder. In addition, cerebral cortical edema, telangiectasia, nerve cell degeneration and necrosis appeared in the irradiated area, which were similar to clinical changes. The primate model prepared by this photothrombosis method is simple and fast. The method provides important tools for neuroprotective research and exhibits important clinical significance. Yang established the photothrombosis model in rhesus monkeys and treated with CircSCMH1-extracellular vesicles which found that it improved neurological deficits after stroke (Li Yang and Honghong, 2020). However, this method is not conducive to the establishment of collateral circulation and ischemia–reperfusion injury, nor is it convenient for observing changes in the ischemic penumbra or the prevention and treatment effects of related drugs. Its ischemia is not permanent but intermittent and is accompanied by a certain degree of reperfusion. The consistency of the thrombus was poor because of the flow of dye.

2.5.2. Endothelin-1 injection model of MCAO

Endothelin-1 (ET-1) is a 21-amino acid peptide with potent and long-acting vasoconstriction properties. It was first identified as an endothelial contractile factor by Yanagisawa in 1988 (Yanagisawa et al., 1988). Researchers have found that ET-1 overrides cerebral autoregulatory mechanisms to constrict a number of cerebral vessels in vivo and reduce cerebral blood flow (CBF) below the ischemic threshold to induce infarction. David first used ET-1 injected in the M2 segment of the MCA in marmosets, which produces a robust M2 territory infarction that is correlated with contralateral motor and sensory/neglect impairments (David Virley et al., 2003). Other studies have also confirmed that endothelin-1 can cause local occlusion of the cerebral arteries in marmoset (Leon Teo, 2014). These studies showed the same result: local injection of endothelin-1 can form a strong contraction of this segment of blood vessels, thereby forming an ischemic state within a certain period of time. When the effect of endothelin fades, blood flow is restored, resulting in ischemia–reperfusion injury. Intracerebral injection of ET-1 into the M1 segment of the middle cerebral artery successfully induced motor cortex infarction in rhesus monkeys (PeiMin Dai et al., 2017). Through MRI, they precisely observed that infarct size reached its peak at 7 days post-operation and then gradually decreased. The endothelin-1-induced cerebral infarction model has good stability and a consistent infarct focus and thus has good application prospects. However, relatively high surgical requirements and precise blood vessel positioning are accompanied by risks of blood vessel rupture and bleeding during injection positioning. Meanwhile, the mechanism by which ET-1 causes cerebral infarction is continuous vasoconstriction and reduced blood flow, but thrombosis is uncertain and not suitable for thrombolytic research. Another problem is that it is difficult to control the consistency of vasoconstriction time. These shortcomings limited its further application.

2.5.3. Ferric chloride-induced model of MCAO

Increasing knowledge of the mechanism of thrombosis in mice has led to the wide use of ferric chloride to induce blood vessel formation thromboembolism. Researchers have found that 10% ferric chloride can induce thrombosis in the mouse middle cerebral artery and that it can be dissolved by tissue-type plasminogen activator (t-PA) (Hulya Karatas et al., 2011). Inducing thrombi in the mouse carotid artery with ferric chloride solution is also feasible (Thomas Bonnard, 2015). Our recent study used ferric chloride solution to induce stable thrombus formation in rat carotid arteries and demonstrated that the thrombus could be dissolved by t-PA (Xiao Lin et al., 2022). Some scholars have tried to use ferric chloride to build a larger artery thrombosis model, such as the canine carotid artery (Allyson et al., 2018). Currently, the main mechanism of ferric chloride-induced thrombosis is to cause local vascular endothelial cells to detach and expose the basement membrane; simultaneously, a large amount of iron ions accumulates on endothelial cells to promote the adhesion of platelets and tissue factors to form aggregates. This triggers the thrombin reaction and leads to thrombus formation (Eckly et al., 2011). Therefore, the thrombus induced by ferric chloride can be dissolved by thrombolytic drugs, which has good application value in thrombolytic drug detection. The size of the thrombus can be adjusted by controlling the filter paper soaked in ferric chloride. The local thrombus formed by ferric chloride is dense and uniform, similar to the thrombus that can form in human blood vessels, with no obvious side effects. Therefore, this method has good application prospects. This method is easy to operate and does not easily cause additional damage; thus, it may appear in the construction of NHP artery thrombosis models in the future.

2.6. Comparison of the above stroke models of nonhuman primates

The multiple different methods mentioned above can produce NHP middle cerebral artery cerebral ischemia models. We have drawn a brief schematic diagram of the main methods (Fig. 1). Each of them has certain advantages and disadvantages. According to the different application directions and operation and implementation capabilities of scholars, all plans have certain application value. We compared the fields in which various monkey brain ischemia model induction methods have been applied in their respective studies in recent years (Table 1). For most research methods, ischemia reperfusion, destruction of brain tissue, imaging changes and neurological deficits are involved, excluding recanalization of blood vessels and thrombi. From the current application results of multiple models, the autologous thrombus injection model and the photothrombosis model could be used in the study of thrombosis. New methods, such as ferric chloride-induced thrombus, are worth considering and have good application prospects.

2.7. Permanent MCAO or transient MCAO

Some of the methods introduced above can be used to build both permanent MCAO models and transient MCAO models. Permanent stroke models usually require physical methods to permanently block major arteries in the brain or leave the emboli that cannot be dissolved by the animal themselves (Jingjing Fan et al., 2017). For example, in the clamp model and electrocoagulation model, when clip is permanently placed to block the blood vessel or the blood vessel is blocked by electrocoagulation, the experimental subjects cannot restore the blood flow through their own strength. If the remaining emboli and clot are stable enough, permanent infarction can also be caused without withdrawing the emboli. Although the mechanisms of vascular occlusion caused by these methods are different, the final outcome will lead to permanent stroke in NHPs. It is suitable for simulating exceed the thrombolysis time window (most patients) or patients with failed thrombectomy, for studying the treatment and rehabilitation process after permanent stroke. As the transient MCAO models, the most popular used methods are endovascular stroke model (balloon), intraluminal filament model and clamp model (Di Wu et al., 2017). Because these three methods can achieve accurate ischemia time and reperfusion time, so as to simulate the ischemia-reperfusion situation of patients after complete thrombolysis at any point time. When the occlusion time reaches the requirement of ischemia, the balloon, suture and clamp are removed to restore blood flow and simulate the effect of timely thrombolysis after stroke. Subsequent studies related to ischemia-reperfusion, such as reducing ischemia-reperfusion injury, and rescue brain tissue which in the ischemic penumbra (IP) area.

3. Imaging evaluation methods and neurological evaluation of nonhuman primates after cerebral ischemic stroke

3.1. Imaging evaluation of postoperative blood flow and infarct focus

Imaging evaluation is also important for assessing NHP models. Imaging evaluation methods, including DSA, MRI, computed tomography (CT), positron emission tomography (PET) and transcranial doppler blood flow (TCD) detection, are required to confirm the success of constructed cerebral ischemia models. These methods show changes in vascular occlusion and cerebral ischemia. MRI is the most common imaging method for evaluating the success of the NHP ischemia model. This method can visually show the size of ischemic infarction and the volume involved. Liu used MRI to detect transient and permanent cerebral infarctions after middle artery occlusion in rhesus monkeys (Yutong Liu et al., 2007). Similarly, diffusion tensor imaging(DTI) is used to visualize the conductive fibers in the neurofunctional region, and the intracranial blood vessels can be reviewed by MRA, which has many advantages over other examination methods (Jakob Seidlitz et al., 2018). Meanwhile, MRI can test more comprehensive brain function by performing other sequences. Alexander West established the rhesus monkey cerebral ischemia model through the orbital approach and successfully detected cerebral blood flow (CBF), apparent diffusion coefficient (ADC), and DWI items by MRI (Alexander West et al., 2009). In

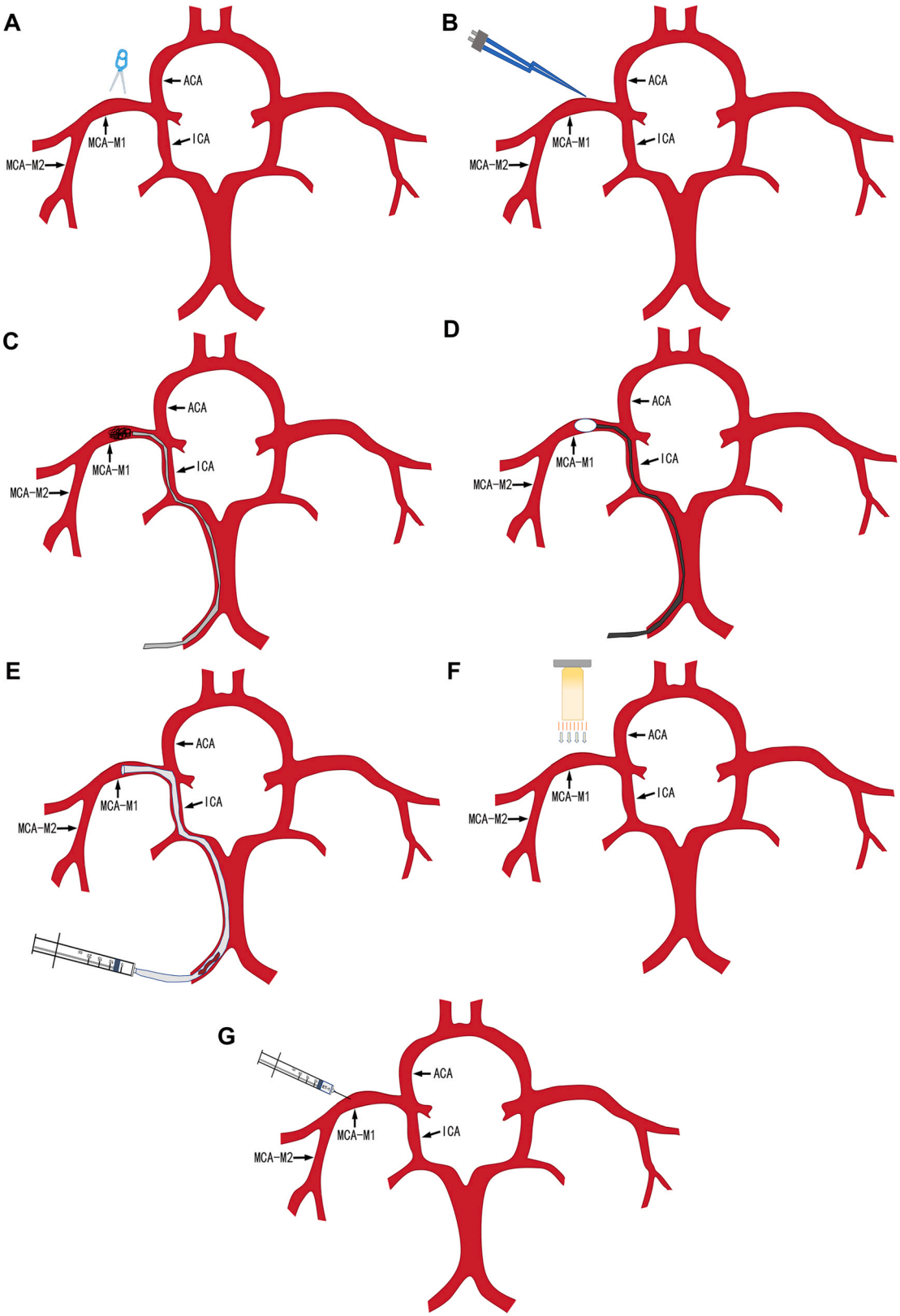

Fig. 1. Schematic diagram of the method for establishing the non-human primate stroke model. A: Clamp model. Using clip to clamp the target artery. B: Electrocoagulation model. Using electrocoagulation to permanently block blood flow of the target artery. C: Endovascular stroke model. Coils are placed after entering the target artery through the catheter. D: Intraluminal filament model. Block the target artery by inserting a suture into the internal carotid artery. E: Autologous thrombus model. After the autologous thrombus is prepared in vitro, positioned the catheter into the target blood vessel and injected autologous thrombus by saline. F: Photothrombosis model. After intravenous injection of Rose-Bengal, a specific light source is used to illuminate the targeted cerebral blood vessels. G: Endothelin-1 injection model. Inject ET-1 into the target artery by using a microinjection.

Table 1
Application Fields and Operation Requirement in Different Construction Methods.

Methods	Applicable field	Operation	Reference
Clippings	Ischemia reperfusion; Permanent infarction; Neurological deficit	Transorbital approach or Transcranial operation	(WR and Garcia, 1970; L S, 1975; Liu et al., 1992; Alan et al., 1997; Stephanie et al., 2008; Bruno et al., 2019; Henry et al., 2017; Douglas et al., 2012)
Electrocoagulation	Permanent infarction; Neurological deficit	Transcranial operation	(Ridley, 1996, 2003; Xinran Chena et al., 2015)
Balloon compression model	Ischemia reperfusion	Transcranial operation	(Spetzler et al., 1980)
Snare ligature model	Ischemia reperfusion; Repeatable stroke model in Awake condition	Transorbital approach	(Crowell et al., 1981)
Endovascular stroke model	Ischemia reperfusion; Permanent infarction	Intervention	(By et al., 1974; Makoto Sasaki et al., 2010; Di Wu et al., 2016; Huanmin Gao et al., 2006)
Intraluminal filament model	Ischemia reperfusion; Neurological deficit	Intervention	(Thomas Freret et al., 2007; Bihel Ebeline et al., 2009)
Autologous thrombus model	Thrombosis; Thrombolysis; Ischemia reperfusion; Permanent infarction; Neurological deficit	Intervention	(Go Kito et al., 2001; Di Wu et al., 2016; Tetsuya Yoshikawa et al., 2008; Teruo Susumu et al., 2006; Longfei Wu et al., 2020; Siying Song et al., 2021)
Photothrombosis model	Thrombosis; Thrombolysis; cyclical flow reduction; Neurological deficit	Transcranial operation	(Masashi Maeda et al., 2005; Atsuyuki Tomizawa et al., 2015)
Endothelin-1 injection model	Thrombosis; Thrombolysis; Neurological deficit	Transcranial operation	(David Virley et al., 2003; Leon Teo, 2014; PeiMin Dai et al., 2017)
Ferric-chloride induced thrombus	Thrombosis; Thrombolysis; Neurological deficit	Not applied	(Hulya Karatas et al., 2011; Thomas Bonnard, 2015; Xiao Lin et al., 2022; Allyson et al., 2018)

the acute ischemic stroke (AIS), the infarcts shown by MRI does not represent the final infarct volume. And sometimes T1-MRI, T2-MRI and FLAIR-MRI are fails to show the infarct areas (within 4.5 h) (Martin Ebinger et al., 2010). DWI and perfusion imaging (PWI) can reflect ischemic changes in brain tissue in the early hours after stroke. Therefore, after establishing a non-human primate stroke model, it is more appropriate to use DWI and PWI to detect infarct lesions in the acute stage, especially within a few hours after a stroke. Fang detected a clear infarct area by DWI at 3 h after stroke in rhesus monkeys, and found that administration of Tat-CIRP could reduce the brain infarct volume and preserve neurological function (Zongping Fang et al., 2021). Wu and his colleagues demonstrated that when an autologous blood clot was used to block the middle cerebral artery in rhesus monkeys, administration of t-PA at 2.5 h after stroke presented different thrombolytic outcomes according to the result of DSA; complete thrombolysis, partial thrombolysis, unable to dissolve thrombolysis (Di Wu et al., 2020). Meanwhile, the results demonstrate that t-PA can be effectively combined with selective intra-arterial cooling (SI-AC) to improve both structural and functional recovery after NHPs stroke (Di Wu et al., 2020). This result is clearly presented by DWI detection in the acute stage at 4 h after stroke. However, sometimes MRI results may exist DWI/PWI mismatch (Mark et al., 2002). Current studies believe that there is an obvious ischemic penumbra area after ischemic stroke. Although these areas are affected by decreased blood flow, the portion of the ischemic territory that is still potentially salvageable, if an appropriate treatment is given (Fisher, 2004). Some researchers think mismatch between the larger hypoperfused area(PWI areas) and the smaller ischemic lesion(DWI areas) on MRI shows the ischemic penumbra (Stephen Davis et al., 2012), timely post-stroke treatment can reduce the damage in this area which is necessary. Cook used the clamp model to establish a macaque stroke model and confirmed the mismatch between the DWI and PWI after surgery 3 h. While using Tat-NR2B9c (a neuroprotective agent) to treat macaque after stroke, the confirmed ischemic penumbra which is DWI/PWI mismatched can be rescued (Douglas et al., 2012). In the chronic stage after stroke, both FALIR-MRI and T2-MRI can show the corresponding infarct area(Di Wu et al., 2020; Hyeon-Gu Yeo et al., 2019). Some researchers have found that functional magnetic resonance imaging (fMRI) signal is importance for prognosis in the subacute disease period of stroke patients, which also could be used for assessment of rehabilitation (Anetta Lasek-Bal et al., 2017; Silvia Del Din et al., 2014). Although the application of fMRI to non-human primates after stroke has not yet been found. However, some studies have begun to focus on fMRI signal changes in the awake, behaving NHPs, especially when video and image stimuli are given, it can be combined with the detection of fMRI to assess the changes in neural activity (Chia-Chun Hung et al., 2015; Leopold, 2015). We believe that in the future, there will be new studies using fMRI to detect the changes of brain state in non-human primate before and after stroke. And using fMRI to detect neural repair in damaged areas during use of effective rehabilitation therapy after stroke is possible. Therefore, after a NHP stroke model is established, it is necessary to select an appropriate sequence when applying MRI to detect infarcts for acute ischemic stroke and chronic ischemic stroke. The shortcomings of MRI are also obvious: it is expensive, and the animal must be anesthetized throughout the process, anesthesia accident may occur due to prolonged examination. DSA can clearly show the interruption in blood flow after cerebrovascular thrombosis or vascular occlusion but not the overall effect of postoperative cerebral ischemic infarction (Yingqian Zhang et al., 2016). The method is suitable for judging whether the blood vessel is occluded during modeling. The disadvantage is that a professional technician is required to perform the operation, and there may be a risk of vascular rupture. PET can quantify regional cerebral blood flow, regional fractional oxygen extraction, and regional oxygen metabolic rate. With these variables, irreversible tissue damage and perfusion after stroke can be clearly defined, which show the potentially salvageable areas (Weber, 2016). However, the complex logistics limit it applications, and at the same time, it is too expensive as an experimental detection tool, few studies currently use PET detection alone for study of non-human primates after stroke. TCD can visually display the changes in blood flow during the operation to determine whether the embolization is complete. It is the most intuitive method of detection during surgery (Bincheng Wang et al., 2016). However, the equipment is expensive and relatively complicated to operate. For the sake of a smaller brain size in monkeys, CT scans might not be clear enough; moreover, MRI can recover the function of CT imaging to a certain extent, so there are few studies using CT alone to evaluate cerebral infarction after brain surgery in NHPs.

Collectively, there are relatively few imaging methods for evaluating vascular occlusion and cerebral infarction in NHPs. Combined application of MRI, DSA and TCD imaging, as well as DWI, DTI, and MRA, are increasingly used to show changes in cerebral ischemic infarction and vascular obstruction (Bo Zhao et al., 2014).

3.2. Neurological evaluation after stroke of nonhuman primates

NHPs stroke, except for imaging examination to determine the formation of infarcts and vascular embolism, also needs behavioral evaluations to prove the corresponding neurological damage. However, the current neurobehavioral testing items for NHPs are not clearly unified, and the testing standards are also quite different. Here, we present several evaluation methods that are currently used in many applications.

3.2.1. Nonhuman primate stroke scale

The NHP stroke scale (NHPSS) score (Table 2) is a comprehensive assessment method with 11 items of NHPs. The assessment includes consciousness, defense response, grip reflex, limb movement, gait, rotation, slow movement, balance, neglect, vision cutting/hemianopia, and facial weakness. This test is included in the stroke scoring system of the National Institutes of Health. Out of a total of 41 points, 0 points corresponded to normal behavior, while 41 points corresponded to severe neurological impairment (Douglas et al., 2012).

NHPSS declares that NHPs can clearly reflect the contralateral side, limbs, vision, and touch caused by the corresponding middle cerebral artery ischemic infarction after induced ischemia. The impact of the changes in perception is more comprehensive for postoperative neurological function evaluation. However, there are still some shortcomings, such as differences in the severity of each score not being particularly obvious, some items may have inaccurate scores, and the test is not applicable if animals had their eyeballs removed.

3.2.2. The neurological deficit score in monkeys after stroke (neurological scale for middle cerebral artery infarction)

The neurological deficit score can be applied to many types of NHPs, such as macaques, cynomolgus monkeys, and rhesus monkeys. This test addresses consciousness, sensory system, motor system, and body skeletal muscle coordination to evaluate neurological impairment in monkeys after cerebral ischemia (Table 3) (Ming Feng et al., 2010).

The evaluation content of the neurological deficit score sheet of stroke monkeys mainly focuses on the consciousness state of neurological function, physical activity, and coordination. Visual field evaluation and spatial orientation are not involved. Detailed scoring criteria and clearly defined scoring items help to evaluate neurological damage accurately in monkeys after cerebral ischemia. However, a large

Table 2
NPHSS.

Stroke clinical rating scale	Content	Points
State of consciousness (0–2)	Normal	0
	Drowsy or apathetic	1
	Unconscious	2
Defense reaction (0–2)	Normal	0
	Diminished	1
	None	2
Grasp reflex (right/left) (0–1 *2):	Present	0
	Absent	1
Extremity movement (upper/lower, right/left) (0–4 *4):	Normal	0
	Asymmetrical use or strength noted	1
	Clear, marked weakness	2
	Minimal movement, profound weakness	3
	No voluntary use and no use in response to stimulation	4
Gait (0–3)	Normal	0
	Limping	1
	Severely impaired	2
	Does not walk (but may crawl)	3
Circling (0–2)	Normal behavior	0
	Noticeable preference to turn to one side	1
	Constant rotation	2
Bradykinesia (0–2)	None	0
	Mild	1
	Severe	2
Balance (0–2)	Normal	0
	Mildly impaired	1
	Profoundly impaired, unable to stand on two feet	2
Neglect (right/left) (0–2 *2)	No neglect	0
	Extinction of stimulus to one side when presented with simultaneous stimuli	1
	Complete neglect of all stimuli, visual, auditory and tactile, presented to the affected side	2
Visual field cut/hemianopsia (right/left) (0–1 *2)	None	0
	No response to visual stimuli in the affected field. Differentiated from neglect by the absence of blinking reflex (does not differentiate cortical lesion, but diagnosed optic tract or optic radiation injury as opposed to cortical problem)	1
Facial weakness (right/left) (0–2 *2)	No weakness	0
	Mild	1
	Profound (if central 7th – constant drooling, hanging angle of mouth)	2

Table 3
Neurological Scale for Middle Cerebral Artery Infarction.

Category	Score
Consciousness (range 0–28)	
Normal consistently alert	0
Conscious and aggressive	4
Conscious and escape	6
Conscious but clouded and accepting	8
Drowsiness, aroused with stimulation	10
Lethargia, eyes open by strong stimulation	16
Stuporous, aroused with persistent stimulation	20
Light coma, reflex movement only	24
Deep coma, no movement	28
Sensory system (range 0–22)	
Facial sensation (ipsi-/contralateral)	
Reacts consistently to touch in any area of face	0/0
Absent, does not react to touch in any area of face	3/3
Pinna reflex (ipsi-/contralateral)	
Twitches ear in response to outer/inner hairs	0/0
Absent, does not move ear in response to touch	3/3
Pain reflex (lower limb, ipsi-/contralateral)	
Strong, quick, complete withdrawal from toe pinch	0/0
Weak, slow, incomplete, or inconsistent withdrawal from toe pinch	3/3
Absent, no withdrawal from toe pinch	5/5
Motor system (range 0–32)	
Hand (motor power/movement, ipsi-/contralateral)	
Normal	0/0
Reduced strength/skilled	2/2
Paralysis/useless	4/4
Leg (motor power/movement, ipsi-/contralateral)	
Normal	0/0
Raises with flexion of knee/against gravity	2/2
Can move, but not against gravity/impossible	4/4
Paralysis/useless	6/6
Upper limb tone (ipsi-/contralateral)	
Normal	0/0
Overtly spastic or flaccid	3/3
Lower limb tone (ipsi-/contralateral)	
Normal	0/0
Overtly spastic or flaccid	3/3
Skeletal muscle coordination (range 0–18)	
Normal, walks normally	0
Minimal ataxia, walks with some impairment of gait	4
Ataxia, but able to climb the wire net	6
Stands spontaneously, falls with a few steps	10
Sits, just able to circle	12
Posed lateral or dorsal recumbency	16
No movement	18
Total	100

evaluation content requires professional behavior evaluation personnel and more careful records.

3.2.3. Standard neurological scale

Spetzler first introduced this neurological test to study NHPs in 1980. This method mainly examines motor function, along with behavioral changes and eye and cranial nerve damage (Spetzler et al., 1980; Helen et al., 2006). The innovative test content is listed in Table 4.

3.2.4. Comparison of the above three neurological evaluation methods and prospect

Through comparison and integration of the above three neurological evaluation methods (Tables 2–4), we presented a comprehensive evaluation (Table 5), which can more intuitively reflect the advantages and disadvantages of each scoring table. This evaluation can help scholars choose the appropriate behavioral evaluation method according to their own experimental programs and surgical methods. In short, NHPSS is suitable for the overall neurological assessment after stroke. It has a good evaluation of the NHP overall motor balance and the ability to respond to stimuli, but it has defects in the detailed evaluation of the fine movements of the limbs, such as the movements of the fingers. The neurological scale for middle cerebral artery infarction provides a more detailed evaluation of the movement of the finger joints, but it lacks visual evaluation, and the content is complex. The standard neurological scale can simply reflect movement and balance after a stroke, but it is not comprehensive and sometimes requires other evaluation methods as a supplement. To the abovementioned three commonly used NHP poststroke behavioral overall scores, there are also some separate evaluation items that test the limb mobility and space exploration ability of NHP animals, such as the hill and valley task, two-tube task, and six-well task (Ridley, 2003; Marshall Ajc et al., 2000). However, it requires some special cages and props that limit its application so that it is sometimes used to supplement the above three evaluations. In addition, a newly scoring method called modified primate Rankin Scale (pRS) was introduced for NHPs (Table 6), which was quite different from NHPSS or neurological scale in evaluation of middle cerebral artery infarction and standard neurological scale, and focus on neurological impairment about their daily activities in chronic stage of NHPs after stroke (Di Wu et al., 2020). Di Wu et al. (2020). As a simple and reliable functional test, this method is similar to modified Rankin Scale (mRS) for human, and can be used for evaluating long-term neurological defect in NHPs.

4. Ethical considerations and the rule of 3R

Although NHP is the closest animal model to humans, the ethical challenges of this type of experimental animal and the rule of 3 R (Reduction, Refinement, Replacement) must be carefully considered when establish a NHP stroke model (Flecknell, 2002). No matter what method is used to establish a stroke model in NHPs, invasive surgery or craniotomy should be involved, but the traumatic pain caused by operation must be eliminated or minimized. And in the postoperative observation period, pain, distress or emotional anxiety due to neurological deficits after ischemic stroke should be minimized as much as possible. Intensive veterinary care must be provided for post-operative NHPs, along with appropriate pain relief, environmental improvement, anti-edema, and antibacterial treatment (Di Wu et al., 2017). If post-stroke animals are unable to feed themselves in the short term, parenteral nutrition should be considered. Another key question is how to control the number of non-human primates used for NHP models to the minimum required for the experiment, thereby reducing abuse of non-human primates. Here, we recommend that researchers can address this issue by consulting with a biostatistician and institutional animal care and use committees before conducting experiments. At the same time, prepare elaborately before the model is established to minimize the operative mortality. It is better to Follow the guidelines for planning animal research and testing during the period of project (Adrian et al., 2018). In addition, researchers should follow the recommendations of the Stroke Therapy Academic Industry Roundtable (STAIR) which instructs that stroke recovery in NHPs should only be performed when enough evidence of efficacy has been obtained from the research of rodent models (Marc Fisher et al., 2009).

Table 4
Standard Neurological Scale.

Category		Score
Motor function (maximum 70)	Severe hemiparesis	10
	Mild hemiparesis	25
	Normal strength – favors opposite extremity	55
	Normal strength – normal function	70
Behavior (maximum 20)	Dead	0
	Coma	1
	Aware of surroundings – moves in response to examiner	5
	Normal aggression – swings on cage bars	10
	Paretic (partial or one-sided paralysis)	15
	Absent	20
Facial paresis (maximum 5)	Complete blindness	0
		5
Visual field (maximum 5)		0
	Hemianopia (blind in 1/2 of field)	1
	Normal visual field	5
		Total maximum 100

Table 5
Comparison of NHPSS, Neurological Scale for Middle Cerebral Artery Infarction and Standard Neurological Scale.

Score content	NHPSS	Neurological Scale for Middle Cerebral Artery Infarction	Standard Neurological Scale
Awareness	√	√	√
Movement	√	√	√
Behavior	√	√	√
Defensive	√	√	√
Fine movement of limbs	×	√	×
Vision	√	×	×
Feel	√	√	×
Balance	√	√	√
Facial reaction	√	√	√
Disadvantage	The evaluation is comprehensive but simple, and the division of the scoring rules is not clear.	The evaluation is comprehensive and complex, lacks visual testing, and requires professional testers and video re-evaluation.	The scoring content is simple, the division is not clear, with insufficient evaluation content.

Table 6
Modified Rankin Scale for nonhuman primate(pRS).

pRS	
0	No symptoms
1	No significant disability; less use and reduced strength of the affected arm; carry out all usual activities; normal mobility
2	Slight disability; unable to grasp with the affected arm; preserve ability to self-cleaning; normal mobility
3	Moderate disability; unable to grasp with the affected arm; slightly limp; less self-cleaning; less mobility
4	Moderately severe disability; unable to walk without assistance; unable to self-cleaning; overall decreased response to stimuli
5	Severe disability, unable to eat or drink; in comma or death

5. Perspectives and other large animal models

As highlighted throughout this review, NHP animal models provide significant benefits in improving clinical translation including the utilization of imaging technologies (such as MRI, DSA), neurological dysfunction after stroke, study of thrombolysis and ischemic penumbra. The advantages and disadvantages are summarized in Table 7. When consider to select the NHPs to establish stroke models, researchers must assessment whether they can meet the high requirements of surgical skills, professional veterinary, behavioral testers and imaging evaluation equipment. Meanwhile, other large animals have also been used for stroke models, such as canines and pigs. Canines have a proportion of gray/white matter so it is more closely to human's brain than small animals. Compared with NHP models, canine model cost less maintenance fees and raises less ethical concerns than that of NHPs (Kunakorn Atchaneeyasakul et al., 2016). The method for establishment of canine stroke model is similar to the method for NHP stroke model, which also covers endovascular stroke model and autologous thrombus model (Cameron Rink et al., 2008; Sheng Liu et al., 2012; Cameron Rink et al., 2011). Researchers have developed a canine stroke score(CSS) which is similar to the National Institute of Health stroke scale (NIHSS) for evaluate the canine neurological function after stroke (Alan et al., 2011). Pig brains are larger than canine brains while presence of obviously cerebral sulci and gyri, and the large intracranial vessel diameter is easy for surgery. The methods for establishment of the pig stroke model include clamp model, electrocoagulation model and autologous thrombus model (Hideaki Watanabe et al., 2007; Simon et al., 2014; Masaharu Sakoh and Gyldensted, 2000; Raul et al., 2012). Because of the large diameter of cerebral vessels in pigs, embolization with emboli (such as coils, guidewires) is not suitable. Stroke models in pigs have fewer fee and ethical concerns, but can also be used to examine post-stroke imaging changes by MRI and DSA (Raul et al., 2012; Matthew et al., 2014). Neurological changes after stroke as assessed by cognitive, memory function and behavioral test in pigs (Elise Titia Gieling and van der Staay, 2011). However, because pigs exhibit high resistance to t-PA, the pig stroke model is contraindicated to study the effect of t-PA combination with other drugs (Makogonenko, 1995). In short, non-human primates are still the best choice of experimental animal stroke models, it is superior to other large animals while meeting the conditions of high fee, precise equipment and professional operators.

6. Conclusion

At present, the application of NHPs in medical research is limited because of economic and ethical factors. Therefore, when using NHPs to study stroke models, it is important to choose the appropriate model methods for study. This article mainly introduces the various methods currently used for constructing NHPs cerebral ischemia models and briefly evaluates and compares their advantages and disadvantages. The craniotomy clamp method and the interventional embolization method that can control the time of blood flow blockade are suitable for the study of ischemia–reperfusion injury, as well as the study of secondary edema and ischemic penumbra. The use of electrocoagulation and other methods to permanently block blood flow is more suitable for the study of neurological deficits caused by long-term cerebral infarction. The photothrombosis model can simulate the effect of intermittent blood flow blockage and is suitable for simulating the symptoms of intermittent blood flow reduction in human vascular stenosis. The autologous thrombus model can be used to study thrombolytic drugs. In addition, evaluation methods of imaging evaluation and neurological deficits methods of NHPs after stroke are also important. Researchers must choose the most suitable method according to the purpose of the experiment. Although there are many kinds of other animal models used for stroke study, the majority of clinical translations is failed. Translation from bench research to bedside treatment of patients with ischemic stroke is a necessity for newer and more effective therapies.

Table 7
Summary of advantages and disadvantages of use NHP establish a stroke model.

Advantages	Disadvantages
Brain structure closer to human.	Difficult to operate.
Corresponding neurological training can be carried out before operation for the evaluation of neurological dysfunction after stroke.	High costs for purchase and feeding the animals.
Post-stroke evaluation can be performed by using relevant clinical imaging evaluation methods (such as MRI、DSA).	Requirement for relevant test equipment with high standard and the testing fee is expensive.
Ability to undertake acute/chronic stroke, ischemic penumbra changed after ischemia-reperfusion.	Ethical considerations higher.
Increased clinical translation.	Required professional veterinarian for animal anesthesia and post-operative care of animals.

The advantages of non-human primates are in longevity, age-related diseases and human-like cognitive abilities, which make them more reliable for clinical translation. In addition, the similar brain structure and suitable for evaluation with imaging tools make it easier to study for human diseases. Therefore, NHPs are important to improve the translation of stroke therapies, the NHP experiment is necessary despite many difficulties.

Funding

This research was funded by grants from the National Natural Science Foundation of China (81820108011 and 81771262), Zhejiang Provincial Natural Science Foundation (2020C03022 and 2017C03027).

CRediT authorship contribution statement

Xiao Lin: Conceptualization, Writing – original draft, Formal analysis. **Hua Wang**: Writing – original draft, Formal analysis. **Jiayu Chen:** Writing – original draft, Formal analysis. **Peiqi Zhao:** Writing – original draft, Formal analysis. **Min Wen:** Writing – original draft. **Lebohang Anesu Bingwa:** Writing – original draft, Formal analysis. **Kunlin Jin:** Writing – review & editing, Funding acquisition. **Qichuan Zhuge:** Conceptualization, Funding acquisition, Formal analysis. **Su Yang:** Conceptualization, Supervision, Project administration. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

Adrian, J., Smith, R.E.C., Elliot Lilley, Aa Hansen, Kristine E., Trond Brattelid, 2018. Prep. Guidel. Plan. Anim. Res. Test. 52, 135–141.
Alan, R., Young, O.T., Jean-Michel Derlon, Giuliano Sette, MacKenzie, Eric T., Jean-Claude Baron, 1997. Early reperfusion in the anesthetized baboon reduces brain damage following middle cerebral artery occlusion. Stroke 28.
Alan, S., Boulos, E.M.D., Dalfino, John C., 2011. Tamoxifen as an effective neuroprotectant in an endovascular canine model of stroke. J. Neurosurg. 114, 1117–1126.
Alexander West, G., KJG, Doyle, Kristian P., Lessov, Nikola S., 2009. A new model of cortical stroke in the rhesus macaque. J. Cereb. Blood Flow. Metab.: Off. J. Int. Soc. Cereb. Blood Flow. Metab. 29, 1175–1186.
Allyson, L., Huttinger, D.G.W., Gnyawali, Surya, Dornbos III, David, Layzer, Juliana M., Nicholas Venetos, Spencer Talentino, Musgrave, Nicholas J., Cheyenne Jones, Camille Bratton, Joseph, Matthew E., Chandan Sen, Sullenger, Bruce A., Nimjee, Shahid M., 2018. Ferric chloride-induced canine carotid artery thrombosis: a large animal model of vascular injury. J. Vis. Exp.
Anetta Lasek-Bal, J.K., Monika Błaszczyszyn, Bartłomiej Stasiów, Amadeusz Żak, 2017. Bold fmri signal in stroke patients and its importance for prognosis in the subacute disease period - preliminary report. Neurol. Neurochir. Pol. 52, 1–6.

Atsuhiro Sugidachi, M.M., Kousaku Ohno, Jakubowski, Joseph A., Atsuyuki Tomizawa, 2016. The active metabolite of prasugrel, r-138727, improves cerebral blood flow and reduces cerebral infarction and neurologic deficits in a non-human primate model of acute ischaemic stroke. Eur. J. Pharmacol. 788, 132–139.
Atsuyuki Tomizawa, K.O., Jakubowski, Joseph A., Mizuno, Makoto, Sugidachi, Atsuhiro, 2015. Prasugrel reduces ischaemic infarct volume and ameliorates neurological deficits in a non-human primate model of middle cerebral artery thrombosis. Thromb. Res. 136, 1224–1230.
Bihel Ebeline, P.-S.P., Letourneur Annelise, Toutain Jerome, Saulnier Romaric, Insausti Ricardo, Bernaudin Myriam, Roussel Simon, Touzani Omar, 2009. Permanent or transient chronic ischemic stroke in the non-human primate: Behavioral, neuroimaging, histological, and immunohistochemical investigations. J. Cereb. Blood Flow. Metab. 30, 273–285.
Bin Cai, N.W., 2016. Large animal stroke models vs. Rodent stroke models, pros and cons, and combination? Acta Neurochir. Suppl. 121 (.), 77–81.
Bincheng Wang, D.W., David Dornbos, I.I.I., Jingfei Shi, Yanhui Ma, Mo Zhang, Yumei Liu, Jian Chen, Yuchuan Ding, Yinghao Luo, Xunming Ji, 2016. Local cerebral hypothermia induced by selective infusion of cold lactated ringer's: a feasibility study in rhesus monkeys. Neurol. Res. 38, 545–552.
Bo Zhao, G.S., Jian Chen, Xiaokun Geng, Xin Ye, Guoxun Xu, Ju Wang, Jiasheng Zheng, Hongjun Li, Fauzia Akbary, Shengli Li, Jing Lu, Feng Ling, Xunming Ji, 2014. A more consistent intraluminal rhesus monkey model of ischemic stroke. Neural Regen. Res. 9, 2087.
Brenchley, J.D.E.S.W.W.J.M., 2018. Nonhuman primate models of human viral infections. Nat. Rev. Immunol. 18, 390–404.
Bruno, P., Meloni, Y.C., Harrison, Kathleen A., Nashed, Joseph Y., Blacker, David J., South, Samantha M., Anderton, Ryan S., Mastaglia, Frank L., Andrew Winterborn, Knuckey, Neville W., Cook, Douglas J., 2019. Poly-arginine peptide-18 (r18) reduces brain injury and improves functional outcomes in a nonhuman primate stroke model. Neurotherapeutics 17, 627–634.
By, G.F., Molinari Jim, Laurent, J.P., 1974. Segmented middle cerebral artery occlusion in primates an experimental method requiring minimal surgery and anesthesia. stroke 5, 334–339.
Cameron Rink, G.C., Amir Abduljalil, Marinos Kontzialis, 2008. Minimally invasive neuroradiologic model of preclinical transient middle cerebral artery occlusion in canines. PNAS 105, 14100–14105.
Cameron Rink, G.C., Khanna, Savita, Peterson, Laura, 2011. Tocotrienol vitamin e protects against preclinical canine ischemic stroke by inducing arteriogenesis. J. Cereb. Blood Flow. Metab. 31, 2218–2230.
Chia-Chun Hung, C.C.Y., Ciuchta, Jennifer L., Daniel Papoti, 2015. Functional mri of visual responses in the awake, behaving marmoset. Neuroimage 15, 1–11.
Christopher, J.L., Murray, T.V.R.L., Mohsen, Naghavi, 2012. Disability-adjusted life years (dalys) for 291 diseases and injuries in 21 regions, 1990–2010 a systematic analysis for the global burden of disease study. Lancet 380, 2197–2223.
Crowell, R.M., FWM, DeGirolami, U., 1981. Variability and reversibility of focal cerebral ischemia in unanesthetized monkey. Neurology 31, 1295–1302.
David Virley, S.J.H., Jenny, C.Roberts, Belinda Farnfield, Heather Elliott, Greg Whelan, Jackie Golder, Chris David, Parsons, Andrew A., Jackie Hunter, A., 2003. A new primate model of focal stroke: endothelin-1—induced middle cerebral artery occlusion and reperfusion in the common marmoset. J. Cereb. Blood Flow. Metab. 24, 24–41.
Di Wu, A.C., Jian Chen, Yuchuan Ding, Xunming Ji, 2017. Endovascular ischemic stroke models in nonhuman primates. Neurotherapeutics 15, 1–10.
Di Wu, J.C., Bincheng Wang, Mo Zhang, Jingfei Shi, Yanhui Ma, Zixin Zhu, Feng Yan, Xiaoduo He, Shengli Li, David Dornbos, I.I.I., Yuchuan Ding, Xunming Ji, 2016. Endovascular ischemic stroke models of adult rhesus monkeys: a comparison of two endovascular methods. Sci. Rep. 6.
Di Wu, J.C., Mohammed Hussain, Longfei Wu, 2020. Selective intra-arterial brain cooling improves long-term outcomes in a non-human primate model of embolic stroke: Efficacy depending on reperfusion status. J. Cereb. Blood Flow. Metab. 0, 1–12.
Di Wu, L.W., Chen, Jian, Huber, Mitchell, 2020. Primate version of modified rankin scale for classifying dysfunction in rhesus monkeys. Stroke 51, 1–4.
Di Wu, Y.F., Longfei Wu, Mitchell Huber, 2020. Reperfusion plus selective intra-arterial cooling (si-ac) improve recovery in a nonhuman primate model of stroke. Neurotherapeutics 1–9.
Douglas, J., Cook, M.T., 2012. Nonhuman primate models of stroke for translational neuroprotection research. Neurotherapeutics 9, 371–379.
Douglas, J., Cook, L.T., Michael Tymianski, 2012. Treatment of stroke with a psd-95 inhibitor in the gyrencephalic primate brain. Nature 483, 213–217.
Eckly, A., BH, Freund, M., Zerr, M., Cazenave, J.-P., Lanza, F., Mangin, P.H., Gachet, C., 2011. Mechanisms underlying fecl3-induced arterial thrombosis. J. Thromb. Haemost.: JTH 9, 779–789.
Elise Titia Gieling, R.E.N., van der Staay, Franz Josef, 2011. Assessing learning and memory in pigs. Anim. Cogn. 14, 151–173.
Fisher, M., 2004. The ischemic penumbra identification, evolution and treatment concepts. Cerebrovasc. Dis. 17, 1–6.
Flecknell, P., 2002. Replacement, reduction and refinement. ALTEX 19 (2), 73–78.
Go Kito, A.N., Teruo, Susumu, 2001. Experimental thromboembolic stroke in cynomolgus monkey. J. Neurosci. Methods 105, 45–53.
Gregg, C., Fonarow, E.E.S., Saver, Jeffrey L., Reeves, Mathew J., 2011. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke. Circulation 123, 750–758.
Gregory, J., Del Zoppo, B.R.C., Harker, Laurence A., 1985. Experimental acute thrombotic stroke in baboons. Stroke 17, 1254–1265.
Haitao Zhu, L.Y., Yayi He, Bo Wang, 2014. Nonhuman primate models of type 1 diabetes mellitus for islet transplantation. J. Diabetes Res. 1–9.
Helen, E., D'Arceuil, M.D., Julian He, Johnny Pryor, Alex de Crespigny, 2006. Middle cerebral artery occlusion in Macaca fascicularis: acute and chronic stroke evolution. J. Med. Primatol. 35, 78–86.
Henry, C.H., SSWS, Law, Quan, Quan, Zhao, Yun, Zhang, Zaijun, 2017. Characterization of the molecular mechanisms underlying the chronic phase of stroke in a cynomolgus monkey model of induced cerebral ischemia. J. Proteome Res. 16, 1150–1166.
Hideaki Watanabe, M.S., Flemming Andersen, Anders Rodell, 2007. Statistical mapping of effects of middle cerebral artery occlusion (mcao) on blood flow and oxygen consumption in porcine brain. J. Neurosci. Methods 160, 109–115.
Huanmin Gao, Y.L., Shaoping Lu, Bo Xiang, Chao Wang, 2006. A reversible middle cerebral artery occlusion model using intraluminal balloon technique in monkeys. J. Stroke Cerebrovasc. Dis. 15, 202–208.
Hulya Karatas, S.E.E., Yasemin Gursoy-Ozdemir, Gunfer Gurer, 2011. Thrombotic distal middle cerebral artery occlusion produced by topical fecl3 application: a novel model suitable for intravital microscopy and thrombolysis studies. J. Cereb. Blood Flow. Metab. 31, 1452–1460.
Hyeon-Gu Yeo, J.J.H., Youngjeon Lee, Kyung Sik Yi, 2019. Increased cd68/tgfβ co-expressing microglia/ macrophages after transient middle cerebral artery occlusion in rhesus monkeys. Exp. Neurobiol. 28, 458–473.
Jakob Seidlitz, C.S., Daniel Glen, Ye, Frank Q., Saleem, Kadharbatcha S., Leopold, David A., Leslie Ungerleider, Adam Messinger, 2018. A population mri brain template and analysis tools for the macaque. NeuroImage 170, 121–131.
Jiamei Lia, H.Z., Ying Liua, Qin Lib, Shan Luc, Ming Fengd, Yanfeng Xua, Lan Huanga, Chunmei Maa, Yihua Ane, Robert Chunhua Zhaob, Renzhi Wangd, Chuan Qin, 2010. Human mesenchymal stem cell transplantation protects against cerebral ischemic injury and upregulates interleukin-10 expression in Macaca fascicularis. Brain Res. 1334, 65–72.
Jiangnan, Hu.S.H., Zhu, Lu, Huang, Weijie, Zhao, Yiping, Jin, Kunlin, ZhuGe, Qichuan, 2018. Tissue plasminogen activator-porous magnetic microrods for targeted thrombolytic therapy after ischemic stroke. ACS Appl. Mater. Interfaces 10, 32988–32997.
Jingjing Fan, Y.L., Xinyu Fu, Lijuan Li, Xiaoting Hao, Shasha Li, 2017. Nonhuman primate models of focal cerebral ischemia. Neural regeneration Res. 17, 321–328.
Jonathan, W.B., Marshall, K.J.D., Richard Green, Ba.A., et al., 2001. Nxy-059, a free radical–trapping agent, substantially lessens the functional disability resulting from cerebral ischemia in a primate species. Stroke 32, 190–198.
Justine Debatisse, O.W., Tae-Hee Cho, Nicolas Costes, Ines Merida, Christelle Leon, 2020. A non-human primate model of stroke reproducing endovascular thrombectomy and allowing long-term imaging and neurological read-outs. J. Cereb. Blood Flow. Metab. 0271678X2092131.
Kunakorn Atchaneeyasakul, L.G., Kevin Ramdas, Mitsuyoshi Watanabe, 2016. Large animal canine endovascular ischemic stroke models: a review. Brain Res. Bull. 127, 1–30.
Kyung Sik Yi, C.-H.C., Sang-Rae Lee, Hong Jun Lee, Youngjeon Lee, Kang-Jin Jeong, Jinwoo Hwang, Kyu-Tae Chang, Sang-Hoon Cha, 2017. Sustained diffusion reversal with in-bore reperfusion in monkey stroke models_ confirmed by prospective magnetic resonance imaging. J. Cereb. Blood Flow. Metab. 37 (6), 2002–2012.
L S, 1975. Experimental model of stroke in the baboon. Adv. Neurol. 10, 199–212.
Leon Teo, J.A.B., 2014. A reproducible and translatable model of focal ischemia in the visual cortex of infant and adult marmoset monkeys. Brain Pathol. 24, 459–474.
Leopold, B.E.R.A.D.A., 2015. Functional mri mapping of dynamic visual features during natural viewing in the macaque. Neuroimage 1, 84–94.
Li Cai, Y.Z., Zhiyong Wang, Yaozu Zhu, 2020. Neuroserpin extends the time window of tpa thrombolysis in a rat model of middle cerebral artery occlusion. J. Biochem. Mol. Toxicol. 34.
Li Yang, B.H., Honghong, Yao, 2020. Extracellular vesicle–mediated delivery of circular rna scmh1 promotes functional recovery in rodent and nonhuman primate ischemic stroke models. Circulation 142, 556–574.
Lisa, A., Miller, C.M.R., Pinkerton, Kent E., Schelegle, Edward S., 2017. Nonhuman primate models of respiratory disease:Past, present, and future. ILAR J. 58, 269–280.
Liu, X.G.B.N., Kawauchi, M., Symon, L., 1992. A model of acture focal ischemia in the territory of the anterior cerebral artery in baboons. Stroke 1, 40–44.
Longa, E.Z., PRW, Carlson, S., Cummins, R., 1989. Reversible middle cerebral artery occlusion without craniectomy in rats. Stroke 20, 84–91.
Longfei Wu, D.I.W., Jian Chen, Chunhua Chen, Tianqi Yao, Xiaoduo He, Yanqin Ma, Xinglong Zhi, Renyu Liu, Xunming Ji, 2020. Intranasal salvinorin a improves neurological outcome in rhesus monkey ischemic stroke model using autologous blood clot. J. Cereb. Blood Flow. Metab. 0271678X2093813.
Maarten, G., Lansberg, E.Ba.V.N.T., 2009. Efficacy and safety of tissue plasminogen activator 3 to 4.5 h after acute ischemic stroke. Stroke 40, 2438–2441.
Makogonenko, M., 1995. SAYMVRVIIE. Activating effect of the plasminogen activators on plasminogens of different mammalia species. Thromb. Res. 79, 423–428.
Makoto Sasaki, K.K., Kaneyoshi Honjo, Jin-Qing Hu, Hai-Bin Wang, Katsuya Shintaku, 2010. Prediction of infarct volume and neurologic outcome by using automated multiparametric perfusion-weighted magnetic resonance imaging in a primate model of permanent middle cerebral artery occlusion. J. Cereb. Blood Flow. Metab. 31, 448–456.
Marc Fisher, G.F., Howells, David W., Hurn, Patricia D., Kent, Thomas A., Savitz, Sean I., Eng, H.Lo, 2009. Update of the stroke therapy academic industry roundtable preclinical recommendations. Stroke 40, 2244–2250.
Mark, W., Parsons, P.A.B., Jonathon Chalk, 2002. Diffusion- and perfusion-weighted mri response to thrombolysis in stroke. Ann. Neurol. 51, 28–37.
Marshall Ajc, J.W.B., Jackson, D.M., 2000. Clomethiazole protects against hemineglect in a primate model of stroke. Brain Res. Bull. 52, 21–29.

Martin Ebinger, I.G., Michal Rozanski, Peter Brunecker, Matthias Endres, Fiebach, Jochen B., 2010. Fluid-attenuated inversion recovery evolution within 12 h from stroke onset a reliable tissue clock ? . Stroke 41, 250–255.
Masaharu Sakoh, L.R., Gyldensted, Carsten, 2000. Cerebral blood flow and blood volume measured by magnetic resonance imaging bolus tracking after acute stroke in pigs comparison with [15o]h2o positron emission tomography. Stroke 1958–1964.
Masashi Maeda, H.T., Yasuhisa, Furuichi, et al., 2005. Characterization of a novel thrombotic middle cerebral artery occlusion model in monkeys that exhibits progressive hypoperfusion and robust cortical infarction. J. Neurosci. Methods 146, 106–115.
Matthew, S., Conrad, B.P.S., Dilger, Ryan N., Johnson, Rodney W., 2014. A three-dimensional digital segmented and deformable brain atlas of the domestic pig. Plos One 9, 1–6.
Maxime Gauberti, P.O., Pierre Guedin, Anne Balossier, Clément Gakuba, Anne Sophie Diependaele, Laurent Chazalviel, Denis Vivien, Young, Alan R., Véronique Agin, Cyrille Orset, 2012. Thrombotic stroke in the anesthetized monkey (Macaca mulatta): characterization by mri - a pilot study. Cerebrovasc. Dis. 33, 329–339.
Ming Feng, H.Z., Zhaohui Zhu, Junji Wei, Shan Lu, Qin Li, Nan Zhang, Guilin Li, Fang Li, Wenbin Ma, Yihua An, Robert Chunhua Zhao, Chuan Qin, Renzhi Wang, 2010. Serial 18f-fdg pet demonstrates benefit of human mesenchymal stem cells in treatment of intracerebral hematoma: a translational study in a primate model. J. Nucl. Med. 52, 90–97.
Nikolas, G., Toman, A.W.Ga.W.C.L., 2019. Neural repair in stroke. Cell Transplant. 28, 1123–1126.
PeiMin Dai, H.H., Lin, Zhang, et al., 2017. A pilot study on transient ischemic stroke induced with endothelin-1 in the rhesus monkeys. Sci. Rep. 7.
Raul, G., Nogueira, E.I.L., Gounis, Matthew, Siddiqui, Adnan H., 2012. The trevo device preclinical data of a novel stroke thrombectomy device in two different animal. J. NeuroIntervent Surg. 4, 295–300.
Ridley, J.W.B.M.A.R.M., 1996. Assess. Funct. Impair. Perm. Middle Cereb. Artery occlusion a Non-Hum. Primate Species 5, 275–286.
Ridley, J.W.B.Ma.R.M., 2003. Assessment of cognitive and motor deficits in a marmoset model of stroke. ILAR J. 44, 2.
Sheng Liu, W.-X.H., Zu, Qing-Quan, Lu, Shan-Shan, 2012. A novel embolic stroke model resembling lacunar infarction following proximal middle cerebral artery occlusion in beagle dogs. J. Neurosci. Methods 209, 90–96.
Shunichi Fukuda, G.J.D.Z., 2003. Models of focal cerebral ischemia in the nonhuman primate. ILAR J. 44, 96–104.
Silvia Del Din, A.B., Zimi Sawacha, Johanna Jonsdottir, Marco Rabuffetti, Claudio Cobelli, Maurizio Ferrarin, 2014. Assessment of biofeedback rehabilitation in post-stroke patients combining fmri and gait analysis a case study. J. Neuroeng. Rehabil. 11, 1–12.
Simon, R., Platt, S.P.H., Howerth, Elizabeth W., Duberstein, Kylee Jo.J., 2014. Development and characterization of a yucatan miniature biomedical pig permanent middle cerebral artery occlusion stroke model. Exp. Transl. Stroke Med. 6, 1–14.
Siying Song, L.G., Di Wu, Jingfei Shi, 2021. Quantitative proteomic analysis of plasma after remote ischemic conditioning in a rhesus monkey ischemic stroke model. Biomolecules 11, 1–14.
Spetzler, R.F., Weinstein, W.R.S., 1980. Chronic reversible cerebral ischemia evaluation of a new baboon model. Neurosugery 7, 3.
Stephanie, J., Murphy, J.R.K., Wenri Zhang, et al., 2008. Can gender differences be evaluated in a rhesus macaque (Macaca mulatta) model of focal cerebral ischemia? Comp. Med. 58, 588–596.
Stephen Davis, B.C., Soren Christensen, Henry Ma, 2012. Perfusion/diffusion mismatch is valid and should be used for selecting delayed interventions. Transl. Stroke Res 3, 188–197.
Teruo Susumu, T.Y., Yuki Akiyoshi, Ryoichi Nagata, Michihiro Fujiwara, Go Kito, 2006. Effects of intra-arterial urokinase on a non-human primate thromboembolic stroke model. J. Pharmacol. Sci. 100, 278–284.
Tetsuya Yoshikawa, Y.A., Teruo, Susumu, et al., 2008. Ginsenoside rb1 reduces neurodegeneration in the peri-infarct area of a thromboembolic stroke model in non-human primates. J. Pharmacol. Sci. 107, 32–40.
Thomas Bonnard, C.E.H., 2015. Ferric chloride-induced thrombosis mouse model on carotid artery and mesentery vessel. J. Vis. Exp.
Thomas Freret, V.B., Toutain, J. erˆome, Romaric Saulnier, Palma Pro-Sistiaga, Ebeline Bihel, MacKenzie, Eric T., Simon Roussel, Pascale Schumann-Bard, Omar Touzani, 2007. Intraluminal thread model of focal stroke in the non-human primate. J. Cereb. Blood Flow. Metab. 28, 786–796.
Tong, F.C., XZ, Kempf, D.J., Yepes, M.S., Connor-Stroud, F.R., Zola, S., Howell, L., 2015. An enhanced model of middle cerebral artery occlusion in nonhuman primates using an endovascular trapping technique. ORIGINAL Res. Interv. 36, 2354–2359.
Valery, L., Feigin, R.V.K., 2015. Priya Parmar, Bo Norrving, George A. Mensah, Derrick A. Bennett, Suzanne Barker-Collo. Update on the global burden of ischemic and hemorrhagic stroke in 1990-2013: The gbd 2013 study. Neuroepidemiology 45, 161–176.
Weber, W.-D.H.A.O.Z., 2016. Validation of mri determination of the penumbra by pet measurements in ischemic stroke. J. Nucl. Med. 58, 1–20.
WR, Garcia, J.-H.H., 1970. Transorbital approach to the middle cerebral artery of the squirrel monkey : a technique for experimental cerebral infarction applicable to uhrastructural studies. Stroke 1 (2), 107–111.
Xiao Lin, P.Z., Zhongxiao Lin, Jiayu Chen, Lebohang Anesu Bingwa, Felix Siaw-Debrah, Peng Zhang, Kunlin Jin, Su Yang, Qichuan Zhuge, 2022. Establishment of a modified and standardized ferric chloride-induced rat carotid artery thrombosis model. ACS Omega 7, 8919–8927.
Xiaodong Zhang, F.T., Chun-Xia Li, Yumei Yan, Doty Kempf, Govind Nair, Silun Wang, Chris Muly, E., Stuart Zola, Leonard Howell, 2015. Temporal evolution of ischemic lesions in nonhuman primates a diffusion and perfusion mri study. PLOS ONE 15.
Xinran Chena, G.D., Chao Danga, Gang Liua, Shihui Xinga, Yicong Chena, Qiang Xub, Jinsheng Zeng, 2015. An ischemic stroke model of nonhuman primates for remote lesion studies: A behavioral and neuroimaging investigation. Restor. Neurol. Neurosci. 33, 131–142.
Yanagisawa, M.K.H., Kimura, S., 1988. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. Nature 332, 411–415.
Yingqian Zhang, F.F., Guojun Zeng, Linlin Zhou, Yinbing Zhang, Jie Zhang, He Jiao, Ting Zhang, Dan Su, Cheng Yang, Xin Wang, Kai Xiao, Hongxia Li, nZhihui Zhong, 2016. Temporal analysis of blood–brain barrier disruption and cerebrospinal fluid matrix metalloproteinases in rhesus monkeys subjected to transient ischemic stroke. J. Cereb. Blood Flow. Metab. 37, 2963–2974.
Yutong Liu, H.E.D.A., MPhil, Susan Westmoreland, Julian He, 2007. Serial diffusion tensor mri after transient and permanent cerebral ischemia in nonhuman primates. Stroke 38, 138–145.
Zongping Fang, D.W., Jiao Deng, Qianzi Yang, 2021. An md2-perturbing peptide has therapeutic effects in rodent and rhesus monkey models of stroke. Sci. Transl. Med 13, 1–11.